Disseminated Intravascular Coagulation
(6th of Feb, 2014)

Done By:
Sara AlArfaj, PharmD candidate KSU
Objectives:

- Brief introduction about DIC
- Explain the pathophysiology of DIC
- Discuss the incidence and etiology of DIC
- Explain the differential diagnosis of DIC
- Highlight the most important options for the management of DIC
- Where does EBM stand in DIC?
Coagulation Cascade
Extrinsic

Tissue factor, VII, IX, VIII

Intrinsic

HMWK, prekallikrein, XII, XI

Common

Thrombin, Fibrinogen, Fibrin
Extrinsic Pathway

- Damage to tissue outside the vessel
  - Tissue Thromboplastin
    - Inactive Factor X
      - Activated Factor X
        - Prothrombin
          - Thrombin
            - Fibrinogen
              - Fibrin
                - Factor XIII
                  - Blood Clot

Intrinsic Pathway

- Damage to the blood vessel
  - Cascade of clotting factors
    - Activated Factor X
What is DIC?

Systemic activation of blood coagulation

Generation of Fibrin

Multiple clot formation

Consumption of coagulation proteins/platelets

Bleeding
DIC itself is not a specific disorder rather than a complication of an underlying disease.
Epidemiology
The overall incidence is difficult to determine

Mortality rates in severe DIC exceeds 75%, depends on primary disease

81% of DIC was associated with SIRS

Overt DIC occurs in 30-50% of patients with Gram negative sepsis

Malignancies account for about 15% of DIC cases

>50% of cases are seen in Obsterical complications

Causes of DIC:

- Sepsis
- Trauma
- Organ destruction
- Toxic / immunological insults
- Severe liver failure
- Malignancies
- Vascular abnormalities
- **Sepsis**
  - Low blood flow and tissue damage
  - Impaired hepatic perfusion
  - Endotoxemia activates factor XII

- **Trauma**
  - Tissue damage
  - Activation of inflammatory mediators and cytokines
  - Activation of hemostatic system

- **Malignancy**
  - Hypercoagulable state
  - Expression by circulation tumor cells
  - Direct activation of factor X
Liver failure
- Decreased synthesis of coagulation proteins
- Impaired clearance of the activated clotting factors

Toxic/Immunological insults
- ABO transfusion incompatibility
- Transplant rejection
- Snake bites
Clinical Manifestations
Acute DIC

- Decompensated DIC
  - Blood exposed to large amounts of tissue factors
  - Over short time
  - Bleeding, renal dysfunction, hepatic dysfunction, respiratory dysfunction, shock, TE and CNS involvement.

Chronic DIC

- Compensated DIC
  - Blood exposed to small amounts of tissue factors
  - More prolonged
  - Asymptomatic, minor thrombosis, minor mucosal or skin bleeding
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Acute DIC</th>
<th>Chronic DIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelet count</td>
<td>Reduced</td>
<td>Variable</td>
</tr>
<tr>
<td>PT</td>
<td>Prolonged</td>
<td>Normal</td>
</tr>
<tr>
<td>aPTT</td>
<td>Prolonged</td>
<td>Normal</td>
</tr>
<tr>
<td>Thrombin Time</td>
<td>Prolonged</td>
<td>Normal</td>
</tr>
<tr>
<td>Plasma Fibrinogen</td>
<td>Reduced</td>
<td>Normal-Elevated</td>
</tr>
<tr>
<td>Factor V</td>
<td>Reduced</td>
<td>Normal</td>
</tr>
<tr>
<td>Factor VIII</td>
<td>Reduced</td>
<td>Normal</td>
</tr>
<tr>
<td>FDPs</td>
<td>Elevated</td>
<td>Elevated</td>
</tr>
<tr>
<td>D-Dimer</td>
<td>Elevated</td>
<td>Elevated</td>
</tr>
</tbody>
</table>
Diagnosis
No specific laboratory test can rule out the diagnosis of DIC

- Acute Vs. Chronic DIC
- Scoring systems
- Differential diagnosis
Platelets

- Thrombocytopenia is a feature in up to 98% of DIC with platelet count < 50 × 10^9 L
- Continuous drop indicates active generation of Thrombin
- Sensitive, but not specific for DIC

PT & aPTT
- Prolonged in 50-60% of cases of DIC
- Reflects components of the Intrinsic and extrinsic pathways
- May be normal or even shorter in some patients

Fibrinogen
- Low in acute decompensated DIC
- Low sensitivity (28%)
- Acute-phase reactant "falsely normal"

FDPs, D-Dimer
- Not specific for DIC
- Most common abnormal parameter in patients with DIC

Markers of Hemostasis
- Antithrombin and Protein C are reduced in DIC
- Neither sensitive nor specific

These Laboratory data are variable in chronic DIC because of a slower rate of consumption of coagulation factors.

- Platelets are slightly reduced
- Fibrinogen is normal or slightly elevated
- PT&aPTT may be within normal ranges

2009 Blackwell Publishing Ltd, British Journal of Haematology, 145, 24–33
Scoring systems:

**ISTH scoring system**
- Strong correlation between increasing score and mortality
- 91% sensitive
- 97% specific

### Table II. ISTH Diagnostic Scoring System for DIC

**Scoring system for overt DIC**

**Risk assessment:** Does the patient have an underlying disorder known to be associated with overt DIC?
- If yes: proceed
- If no: do not use this algorithm

**Order global coagulation tests** (PT, platelet count, fibrinogen, fibrin related marker)

**Score the test results**
- Platelet count (>100 \times 10^9/l = 0, <100 \times 10^9/l = 1, <50 \times 10^9/l = 2)
- Elevated fibrin marker (e.g. D-dimer, fibrin degradation products) (no increase = 0, moderate increase = 2, strong increase = 3)
- Prolonged PT (<3 s = 0, >3 but <6 s = 1, >6 s = 2)
- Fibrinogen level (>1 g/l = 0, <1 g/l = 1)

**Calculate score:**
- ≥5 compatible with overt DIC: repeat score daily
- <5 suggestive for non-overt DIC: repeat next 1–2 d
JAAM DIC scoring system

JAAM criteria seem to have an advantage for selection of patients with early DIC

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic inflammatory response syndrome criteria</td>
<td></td>
</tr>
<tr>
<td>$\geq 3$</td>
<td>1</td>
</tr>
<tr>
<td>0–2</td>
<td>0</td>
</tr>
<tr>
<td>Platelet count (cells/$\mu$L)</td>
<td></td>
</tr>
<tr>
<td>$&lt; 80,000$ or $&gt; 50%$ decrease within 24 hr</td>
<td>3</td>
</tr>
<tr>
<td>$\geq 80,000$ and $&lt; 120,000$ or $&gt; 30%$ decrease within 24 hr</td>
<td>1</td>
</tr>
<tr>
<td>$\geq 120,000$</td>
<td>0</td>
</tr>
<tr>
<td>Prothrombin time (patient’s value/normal value)</td>
<td></td>
</tr>
<tr>
<td>$\geq 1.2$</td>
<td>1</td>
</tr>
<tr>
<td>$&lt; 1.2$</td>
<td>0</td>
</tr>
<tr>
<td>Fibrin/fibrinogen degradation products (mg/L)</td>
<td></td>
</tr>
<tr>
<td>$\geq 25$</td>
<td>3</td>
</tr>
<tr>
<td>$\geq 10$ and $&lt; 25$</td>
<td>1</td>
</tr>
<tr>
<td>$&lt; 10$</td>
<td>0</td>
</tr>
</tbody>
</table>

NOTE: A score of $\geq 4$ indicates a diagnosis of disseminated intravascular coagulation.

Gando et al. Critical Care 2013, 17:R297 Page 4 of 10
Differential diagnosis:

- **Acute DIC Vs. Severe Liver Disease**
  - Marked decreases in levels of factor VIII in DIC
  - Marked increases in D-dimer in DIC

- **DIC Vs. Fibrinogenolysis**
  - Can be distinguished by the absence if elevated D-dimer

- **DIC vs Heparin Induced Thrombocytopenia**
  - Unexplained thrombocytopenia
  - Thrombosis associated with thrombocytopenia
  - 50% or more drop in platelet count
  - Necrotic skin lesions at heparin injection site
Treatment
Management of underlying disease

Blood components and coagulation factors

Anticoagulation

Restoration of anticoagulant pathways
In general..

<table>
<thead>
<tr>
<th>Mild, Asymptomatic, self-limiting with laboratory findings of coagulopathy</th>
<th>• Observe</th>
</tr>
</thead>
</table>
| Patients with DIC bleeding/high risk of bleeding | • Platelets to improve Thrombocytopenia  
• FFP to replace all consumed coagulation factors and correct the prolonged PT and aPTT |
| Additional severe Hypofibrinogenemia (<1 g/L) | • Fibrinogen concentrates or Cryoprecipitate |
Sepsis

 Initial Resuscitation
   Fluid therapy
   Inotropes/Vasopressors
   Corticosteroids

 Source Control
   Abdominal
   Respiratory
   UTI
   Sinuses
   Lines

 Proper Antibiotics

## Blood Components:

<table>
<thead>
<tr>
<th>Platelets</th>
<th>Threshold for transfusing depends on the clinical state</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>➢ Bleeding + platelets $&lt;5 \times 10^9$/L</td>
</tr>
<tr>
<td></td>
<td>➢ Non-bleeding + platelets $10-20 \times 10^9$/L</td>
</tr>
<tr>
<td></td>
<td><strong>Dose</strong>: 1-2 U/10 kg/day</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Plasma</th>
<th><strong>Symptomatic bleeding</strong>:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>➢ INR $&gt;2.0$</td>
</tr>
<tr>
<td></td>
<td>➢ prolonged PT/APTT ($&gt;1.5$ times normal)</td>
</tr>
<tr>
<td></td>
<td>➢ Fibrinogen level $&lt;1$g/L</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Coagulation factors</th>
<th><strong>Prothrombin Complex Concentrate</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>➢ Lacks essential factors (Factor V)</td>
</tr>
<tr>
<td></td>
<td>➢ In patients who can't receive FFP due to overload</td>
</tr>
<tr>
<td></td>
<td><strong>Fibrinogen concentrate or cryoprecipitate</strong></td>
</tr>
<tr>
<td></td>
<td>➢ Actively bleeding patients/hypofibrinogenemia (1g/L)</td>
</tr>
<tr>
<td></td>
<td>➢ 1 unit cryo/5 kg will increase fibrinogen 100 mg/dl</td>
</tr>
<tr>
<td>Coagulation Factor</td>
<td>Amount per Unit</td>
</tr>
<tr>
<td>------------------------------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>150–250 mg</td>
</tr>
<tr>
<td>Factor VIII</td>
<td>80–150 units</td>
</tr>
<tr>
<td>von Willebrand's factor</td>
<td>100–150 units</td>
</tr>
<tr>
<td>Factor XIII</td>
<td>50–75 units</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Coagulation Factor</th>
<th>Concentration</th>
<th>Half-life (hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrinogen</td>
<td>2–4.5 mg/mL</td>
<td>100–150</td>
</tr>
<tr>
<td>Prothrombin (factor II)</td>
<td>~ 1 unit/mL</td>
<td>50–80</td>
</tr>
<tr>
<td>Factor V</td>
<td>~ 1 unit/mL</td>
<td>12–24</td>
</tr>
<tr>
<td>Factor VII</td>
<td>~ 1 unit/mL</td>
<td>6</td>
</tr>
<tr>
<td>Factor VIII</td>
<td>~ 1 unit/mL</td>
<td>12</td>
</tr>
<tr>
<td>Factor IX</td>
<td>~ 1 unit/mL</td>
<td>24</td>
</tr>
<tr>
<td>Factor X</td>
<td>~ 1 unit/mL</td>
<td>30–60</td>
</tr>
<tr>
<td>Factor XI</td>
<td>~ 1 unit/mL</td>
<td>40–80</td>
</tr>
<tr>
<td>Factor XIII</td>
<td>~ 1 unit/mL</td>
<td>150–300</td>
</tr>
<tr>
<td>von Willebrand's factor</td>
<td>~ 1 unit/mL</td>
<td>24</td>
</tr>
</tbody>
</table>

aPTT = activated partial thromboplastin time; PT = prothrombin time.
## Anticoagulation:

<table>
<thead>
<tr>
<th>Heparin</th>
<th>Gabexate mesilate/Nafamostat (synthetic protease inhibitors)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• No RCT indicates the benefit of Heparin in DIC</td>
<td></td>
</tr>
<tr>
<td>• In patients with high risk of bleeding, CI UFH can be used</td>
<td></td>
</tr>
<tr>
<td>• In critically ill, non-bleeding patients with DIC, prophylaxis for VTE with UFH, LMWH or Mechanical methods can be used</td>
<td></td>
</tr>
<tr>
<td>• Used and evaluated in Japan</td>
<td></td>
</tr>
<tr>
<td>• No RCTs showing a reduction in the mortality rate or an improvement in the resolution rate in DIC</td>
<td></td>
</tr>
</tbody>
</table>

2013 International Society on Thrombosis and Haemostasis/2009 Blackwell Publishing Ltd, British Journal of Haematology,
Restoration of Coagulation Pathways:

Antithrombin

- Previous studies showed an improvement of laboratory values and DIC scores, but no effect on mortality.

Activated Protein C

- It was shown to reduce mortality and improve organ dysfunction (PROWESS/ENHANCE).
- Withdrawal of APC from sepsis treatment in 2011 was proposed after an RCT for sepsis shock failed to show any benefit (PROWESS-SHOCK).

Tissue Factor Pathway Inhibitor

- Animal studies have been promising in preventing mortality and end-organ damage.
- Large phase III RCT didn't show any mortality benefit.

Drotrecogin alfa (activated) in the treatment of severe sepsis patients with multiple-organ dysfunction:

Drotrecogin alfa (activated) treatment in severe sepsis from the global open-label trial ENHANCE: further evidence for survival and safety and implications for early treatment.


Author information

Abstract

OBJECTIVE: To provide further evidence for the efficacy and safety of drotrecogin alfa (activated) treatment in severe sepsis.


SETTING: ENHANCE took place in 25 countries at 361 sites.

PATIENTS: Patients with known or suspected infection, three or four systemic inflammatory response syndrome criteria, and one or more sepsis-induced organ dysfunctions. Of 2,434 adults entered, 2,378 received drotrecogin alfa (activated), and of these, 2,375 completed the protocol.

INTERVENTIONS: Drotrecogin alfa (activated) was infused at a dose of 24 mg/kg/hr for 96 hrs.

MEASUREMENTS AND MAIN RESULTS: The 28-day all-cause mortality approximated that observed in PROWESS (25.3% vs. 24.7%). Although patients in ENHANCE had increased serious bleeding rates compared with patients in the drotrecogin alfa (activated) arm of PROWESS (during infusion, 3.6% vs. 2.4%; postinfusion, 3.2% vs. 1.2%; 28-day, 6.5% vs. 3.5%), increased postinfusion bleeding suggested a higher background bleeding rate. Intracranial hemorrhage was more common in ENHANCE than PROWESS (during infusion, 0.6% vs. 0.2%; 28-day, 1.5% vs. 0.2%). The incidence of fatal intracranial hemorrhage was the same during infusion (0.2%) and higher at 28 days (0.5% vs. 0.2%). ENHANCE patients treated within 0-24 hrs from their first sepsis-induced organ dysfunction had lower observed mortality rate than those treated after 24 hrs (22.9% vs. 27.4%, p = .01).

CONCLUSIONS: ENHANCE provides supportive evidence for the favorable benefit/risk ratio observed in PROWESS and suggests that more effective use of drotrecogin alfa (activated) might be obtained by initiating therapy earlier.
Efficacy and Safety of Tifacogin (Recombinant Tissue Factor Pathway Inhibitor) in Severe Sepsis
A Randomized Controlled Trial

Edward Abraham, MD; Konrad Reinhart, MD; Steven Opal, MD; Ignace Demeyer, MD; Christopher Doig, MD, MSc; Angel López Rodriguez, MD; Richard Beale, MD; Petr Svoboda, MD, PhD; Pierre Francois Laterre, MD; Stuart Simon, MD; Bruce Light, MD; Herbert Spapen, MD; Judy Stone, MD; Allan Seibert, MD; Claus Peckelsen, MD; Cathy De Deyne, MD; Russell Postier, MD; Ville Pettitl, MD; Charles L. Sprung, MD, Antonio Artigas, MD; Sandra R. Perel, PhD; Vincent Shu, PhD; Christian Zwingelstein, PharmD; Jeffrey Tobias, MD; Lona Poole, MD; James C. Stolzenbach, PhD; Abla A. Greasy, PhD;

for the OPTIMIST Trial Study Group

**Context**
The expression and release of tissue factor is a major trigger for the activation of coagulation in patients with sepsis. Tissue factor pathway inhibitor (TFPI) forms a complex with tissue factor and blood protease factors leading to inhibition of thrombin generation and fibrin formation.

**Objectives**
To determine if administration of tifacogin (recombinant TFPI) provides mortality benefit in patients with severe sepsis and elevated international normalized ratio (INR) and to assess tifacogin safety in severe sepsis, including patients with low INR.

**Design and Setting**
A randomized, double-blind, placebo-controlled, multicenter, phase 3 clinical trial conducted from March 21, 2000, through September 27, 2001, in 245 hospitals in 17 countries in North America, Europe, and Israel.

**Patients**
The primary efficacy population consisted of 1754 patients (≥18 years) with severe sepsis and a high INR (≥1.2) randomly assigned to intravenous infusion of either tifacogin (0.025 mg/kg per hour for 96 hours, n = 880) or placebo (arginine citrate buffer, n = 874), and 201 patients with a low INR (<1.2) randomly assigned to receive the same dose of either tifacogin or placebo.

**Main Outcome Measure**
All-cause 28-day mortality.

**Results**
Overall mortality at 28 days in the tifacogin-treated group (n = 880) vs the placebo group (n = 874) for high INR was 34.2% vs 33.9%, respectively (P = .88, Pearson χ² test; P = .75, logistic regression model). None of the protocol-specified secondary end points differed between the tifacogin vs placebo groups. An analysis on the first 722 patients demonstrated a mortality rate of 38.9% for placebo vs 29.1% for tifacogin (P = .006, Pearson χ² test). Tifacogin significantly attenuated prothrombin fragment 1.2 and thrombin-antithrombin complex levels (P < .001, 2-sample t test) in patients with high and low INR. Overall mortality was lower in the tifacogin response in patients with low INR (12%; n = 83) vs placebo (22.9%; n = 118) (P = .051, Pearson χ² test; P = .03, logistic regression model). There was an increase in serious adverse events with bleeding in the tifacogin group in both cohorts (6.5% tifacogin and 4.8% placebo for high INR; 6.0% tifacogin and 3.3% placebo for low INR).

**Conclusions**
Treatment with tifacogin had no effect on all-cause mortality in patients with severe sepsis and high INR. Tifacogin administration was associated with an increase in risk of bleeding, irrespective of baseline INR.
Treatment effects of recombinant human soluble thrombomodulin in patients with severe sepsis: a historical control study

Kazuma Yamakawa¹,²*, Satoshi Fujimi¹, Tomoyoshi Mohri¹, Hiroki Matsuda¹, Yasushi Nakamori¹, Tomoya Hirose², Osamu Tasaki², Hiroshi Ogura², Yasuyuki Kuwagata², Toshimitsu Hamasaki³ and Takeshi Shimazu²

Abstract

Introduction: Cross-talk between the coagulation system and inflammatory reactions during sepsis causes organ damage followed by multiple organ dysfunction syndrome or even death. Therefore, anticoagulant therapies have been expected to be beneficial in the treatment of severe sepsis. Recombinant human soluble thrombomodulin (rhTM) binds to thrombin to inactivate coagulation, and the thrombin-rhTM complex activates protein C to produce activated protein C. The purpose of this study was to examine the efficacy of rhTM for treating patients with sepsis-induced disseminated intravascular coagulation (DIC).

Methods: This study comprised 65 patients with sepsis-induced DIC who required ventilatory management. All patients fulfilled the criteria of severe sepsis and the International Society on Thrombosis and Haemostasis criteria for overt DIC. The initial 45 patients were treated without rhTM (control group), and the following 20 consecutive patients were treated with rhTM (0.06 mg/kg/day) for six days (rhTM group). The primary outcome measure was 28-day mortality. Stepwise multivariate Cox regression analysis was used to assess which independent variables were associated with mortality. Comparisons of Sequential Organ Failure Assessment (SOFA) score on sequential days between the two groups were analyzed by repeated measures analysis of variance.

Results: Cox regression analysis showed 28-day mortality to be significantly lower in the rhTM group than in the control group (adjusted hazard ratio, 0.303; 95% confidence interval, 0.106 to 0.871; P = 0.027). SOFA score in the rhTM group decreased significantly in comparison with that in the control group (P = 0.028). In the post hoc test, SOFA score decreased rapidly in the rhTM group compared with that in the control group on day 1 (P < 0.05).

Conclusions: We found that rhTM administration may improve organ dysfunction in patients with sepsis-induced DIC. Further clinical investigations are necessary to evaluate the effect of rhTM on the pathophysiology of sepsis-induced DIC.
Where Does EBM stand in DIC?
New diagnostic strategy for sepsis-induced disseminated intravascular coagulation: a prospective single-center observational study

- Published in Critical Care Journal, Jan 20 2014

- Conducted in a tertiary hospital in Japan between June 2010- June 2011

- Aim was to define a biomarker panel to predict sepsis-induced DIC in ED patients
Method:

- Method: n=84, 2 were excluded, 26 were classified as Sepsis-induced DIC patients.

Inclusion criteria:
- Age ≥ 18, met 1≥ SIRS

Exclusion criteria:
- Who lacked a concentration of biomarkers or apparent clinical manifestations

- 28-day all-cause mortality was assessed, all patients were followed up for 28 days after enrollment.

- Patients were evaluated according to ACCP/SCCM for SIRS and Sepsis.
- JAAM scoring system was used.
- APACHE II for illness severity was used.
- SOFA for organ failure

Table 1 Patient backgrounds

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>JAAM DIC Negative</th>
<th>JAAM DIC Positive</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-infection</td>
<td>8</td>
<td>4</td>
<td>12</td>
</tr>
<tr>
<td>SIRS</td>
<td>15</td>
<td>4</td>
<td>19</td>
</tr>
<tr>
<td>Infection</td>
<td>6</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>Sepsis</td>
<td>5</td>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td>Severe sepsis</td>
<td>4</td>
<td>10</td>
<td>14</td>
</tr>
<tr>
<td>Septic shock</td>
<td>8</td>
<td>13</td>
<td>21</td>
</tr>
<tr>
<td>Total</td>
<td>46</td>
<td>36</td>
<td>82</td>
</tr>
</tbody>
</table>

DIC, disseminated intravascular coagulation; JAAM, Japanese Association for Acute Medicine; SIRS, systemic inflammatory response syndrome.

Table 2 Clinical characteristics of the 26 sepsis-induced DIC patients

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory</td>
<td>10</td>
</tr>
<tr>
<td>Intra- or retro-abdominal, or pelvic cavity</td>
<td>9</td>
</tr>
<tr>
<td>Soft tissue or bone</td>
<td>4</td>
</tr>
<tr>
<td>Urinary</td>
<td>1</td>
</tr>
<tr>
<td>Blood or catheter</td>
<td>1</td>
</tr>
<tr>
<td>Unknown</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>26</td>
</tr>
</tbody>
</table>
Results

Among the 11 biomarkers tested, the optimal 2-marker panel comprised presepsin and protein C.

All secondary outcomes except for mortality were significantly higher depending on the severity (P<0.0001).

- Mild: 7.14%
- Moderate: 15.4%
- Severe: 28.6%

Biomarkers with AUC >0.8 were selected (Presepsin= 0.913 , PC=0.880)

Presepsin: protein that is a truncated N-terminal fragment of CD14, an inflammatory biomarker. Its levels specifically increase in the blood of septic patients.

Protein C: coagulation protein, the activated form (APC) plays an important role in regulation blood clotting, inflammation and cell death.

[Table of biomarkers and normal ranges]
**conclusion**

- The diagnostic criteria proposed herein are very simple, easy to employ, and can be used in ICU as a point-of-care test.
- New sepsis-induced DIC diagnostic criteria were defined as following 3 groups:
  - **Severe**: presepsin >900 pg/mL, PC <45%
  - **Mild**: presepsin <650 pg/mL, PC >45%
  - **Moderate**: ranges between severe and mild groups

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**Table 5 Cut-off values of each biomarker stratified by the presence or absence of sepsis and DIC**

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Sepsis</th>
<th>DIC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cut-off value</td>
<td>Sensitivity</td>
</tr>
<tr>
<td>Presepsin, $\times 10^2$ pg/mL</td>
<td>647</td>
<td>93.0%</td>
</tr>
<tr>
<td>PC activity, %</td>
<td>47</td>
<td>77.5%</td>
</tr>
</tbody>
</table>

DIC, disseminated intravascular coagulation; PC, protein C.
ROC analysis comparing the accuracy for the prediction of 30-day mortality revealed (AUC) for Presepsin, APACHE II score and PCT of 0.878, 0.815 and 0.661, respectively.

PATHFAST® Presepsin "Mitsubishi Chemical Medience Corporation"
A randomized, controlled, multicenter trial of the effects of Antithrombin on disseminated intravascular coagulation in patients with sepsis

- Published in Critical Care Journal, 2013

- By JAAM DIC study group at 13 critical care centers of tertiary care hospitals (April 2008- Feb 2012)

- Primary endpoint was recovery from DIC on Day 3

- Secondary endpoint was 28-day all-cause mortality
Method:

- N= 60, Included patients diagnosed with JAAM DIC score of ≥ 4 with sepsis, levels of AT ranging from 50-80%

- Patients were well matched for age, sex, and APACHE II, SIRS, SOFA and DIC scores.

- Web-based randomization, neither physicians or patients were blinded to the treatment:
  - AT at a dose of 30 IU/Kg for 3 days
  - No intervention
Results:

- JAAM decided to stop the trial based on the results of the interim analysis, due to the strictly established conditions of the control group.

- DIC scores in the AT group (53.3%) significantly improved compared to control group (20.0%).

- 28-day mortality rates of the control and AT group were 13.3 % and 10.0 %, respectively.

- No major bleeding related to AT therapy.
Black circles : AT (n=30)
white squares: control (n=28)
Figure 4 The Kaplan-Meier survival plots for the 30 patients in the control group (squares) and 30 patients treated with antithrombin (circles).
Limitations:

- Small sample size, due to the strict setup conditions in the control group
- Lacks statistical power
- No double-blind placebo-controlled design
- Sepsis, severe sepsis and septic shock were included, but Sepsis ratios were high in both groups
- Generalizability
Conclusion:

- Moderate dose of AT improves DIC scores and brings about a better recovery rate of DIC associated with sepsis.

- Does not improve SOFA scores, has no effect on 28-day mortality in patients with DIC associated with sepsis.

- Provides a rationale for conduction powered RCTs addressing in patients with severe sepsis & septic shock.
To-take home messages

- DIC is a systemic process produces both thrombosis and hemorrhage
- Laboratory values accompanied with the clinical picture are important to diagnose DIC
- Sepsis, trauma and tissue destruction can cause DIC
- Treatment of the underlying cause is of central importance in controlling DIC
- Individualization of supportive modalities
Thank you..

Questions?